REMARKS/ARGUMENTS

Claims 10, 13-16, 18, 31 and 33-37 were pending. Claims 10 and 31 are amended, and Claim 10 has been rewritten in independent form. No new matter is added. Support for the amending language may be found in the specification at page 11, lines 21-25. Reconsideration of the rejections is requested.

Claims 31 and 33-37 have been rejected under 35 U.S.C. 102(e) as anticipated by Winkler *et al.* U.S. Patent no, 5,677,195. Applicants respectfully submit that the presently claimed invention is not anticipated by the cited reference.

The Winkler *et al.* patent is directed to methods of synthesizing polymers on a substrate, or to the use of non-planar substrates, and thus does not teach the invention set forth in Claims 31 and 33-37.

The methods of Winkler *et al.* are designed for the synthesis of polymers on a substrate, and can not be adapted to provide the microarrays taught by Applicants. As stated in the summary of the invention:

> According to the first specific aspect of the invention, a block having a series of channels, such as grooves, on a surface thereof is utilized. The block is placed in contact with a derivatized glass or other substrate. In a first step, a pipettor or other delivery system is used to flow selected reagents to one or more of a series of apertures connected to the channels, or place reagents in the channels directly, filling the channels and "striping" the substrate with a first reagent, coupling a first group of monomers thereto. The first group of monomers need not be homogenous. For example, a monomer A may be placed in a first group of the channels, a monomer B in a second group of channels, and a monomer C in a third group of channels. The channels may in some embodiments thereafter be provided with additional reagents, providing coupling of additional monomers to the first group of monomers. The block is then translated or rotated, again placed on the substrate, and the process is repeated with a second reagent, coupling a second group of monomers to different regions of the substrate. The process is repeated until a diverse set of polymers of desired sequence and length is formed on the substrate. By virtue of the process, a number of polymers having diverse monomer sequences such as peptides or oligonucleotides are formed on the substrate at known locations.

This method of *in situ* synthesis of the polymer is further supported by the citations to the patent provided in the Office Action. It is stated in the Office Action that the patent teaches an array comprising 1000 or more discrete regions of distinct polypeptides/cm^2 at column 17, lines 49-58. However, the cited section cannot be understood in isolation, as the preceding paragraphs explain the invention in more detail. Specifically, it can be seen from the preceding columns that the described invention relates to the synthesis of polymers *in situ*.

A particularly preferred channel block is prepared by chemical etching of polished silicon wafers. Chemical etching is a widely used technique in integrated circuit fabrications. It can easily provide 60 or more 100 micron channels on a 12.8 mm region of a polished silicon wafer. Even after etching, the top (unetched) surface regions of the wafer retains the very flat profile of the unetched wafer. Thus, close contact with the substrate is ensured during flow cell operation.

In operation, the surface of the substrate is appropriately treated by cleaning with, for example, organic solvents, methylene chloride, DMF, ethyl alcohol, or the like. Optionally, the substrate may be provided with appropriate linker molecules on the surface thereof. The linker molecules may be, for example, aryl acetylene, ethylene glycol oligomers containing from 2–10 monomers or more, diamines, diacids, amino acids, or combinations thereof. Thereafter, the surface is provided with protected surface active groups such as t-butoxycarbonyl (TBOC) or 9-fluorenylmethoxycarbonyl ("FMOC") protected amino acids. Such techniques are well known to those of skill in the art.

Thereafter, the channel block and the substrate are brought into contact forming fluid-tight channels bounded by the grooves in the channel block and the substrate. When the channel block and the substrate are in contact, a protecting group removal agent is, thereafter, directed through a first selected channel or group of channels by placing the pipettor on the flow inlet of the selected channel and, optionally, the vacuum source on the outlet of the channel. In the case of, for example, TBOC protected amino acids, this protecting group removal agent may be, for example, trifluoroacetic acid (TFA). This step is optionally followed by steps of washing to remove excess TFA with, for example, dichloromethane (DCM).

Thereafter, a first amino acid or other monomer A is directed through the first selected flow channel. Preferably this first amino acid is also provided with an appropriate protecting group such as TBOC, FMOC, nitroveratryloxycarbonyl ("NVOC"), or the like. This step is also followed by appropriate washing steps. The of deprotection/coupling steps employed in the first group of channels are concurrently with or thereafter repeated in additional groups of channels. In preferred embodiments, monomer A will be directed through the first group of channels, monomer B will be directed through a second group of flow channels, etc., so that a variety of different monomers are coupled on parallel channels of the substrate.

Thereafter, the substrate and the channel block are separated and, optionally, the entire substrate is washed with an appropriate material to remove any unwanted materials from the points where the channels contact the substrate.

The substrate and/or block is then, optionally, washed and translated and/or rotated with the stage. In preferred embodiments, the substrate is rotated 90 degrees from its original position, although some embodiments may provide for greater or less rotation, such as from 0 to 180 degrees. In other embodiments, such as those discussed in connection with the device shown in FIG. 7, two or more different channel blocks are employed to produce different flow patterns across the substrate. When the channel block is rotated, it may simultaneously be translated with respect to the substrate. "Translated" means any relative motion of the substrate and/or channel block, while "rotation" is intended to refer to rotation of the substrate and/or channel block about an axis perpendicular to the substrate and/or channel block. According to some embodiments the relative rotation is at different angles for different stages of the synthesis.

The steps of deprotection, and coupling of amino acids or other monomers is then repeated, resulting in the formation of an array of polymers on the surface of the substrate. For example, a monomer B may be directed through selected flow channels, providing the polymer AB at intersections of the channels formed by the channel block in the first position with the channels formed by the channel block after 90-degree rotation.

While rotation of the channel block is provided according to preferred embodiments of the invention, such rotation is not required. For example, by simply flowing different reagents through the channels, polymers having different monomer sequences may be formed. Merely by way of a specific example, a portion of the channels may be filled with monomer "A," and a portion filled with monomer "B" in a first coupling step. All or a portion of the first channels are then filled with a monomer "C," and all or a portion of the second channels are filled with a monomer "D," forming the sequences AB and CD. Such steps could be used to form 100 sequences using a basis set of 10 monomers with a 100-groove channel block.

In another embodiment, the invention provides a multichannel solid-phase synthesizer as shown in FIG. 12. In this embodiment, a collection of delivery lines such as a manifold or collection of tubes **1000** delivers activated reagents to a synthesis support matrix **1002**. The collection of tubes **1000** may take the form of a rigid synthesis block manifold which can be precisely aligned with the synthesis support matrix **1002**. The support matrix contains a plurality of reaction regions **1004** in which compounds may be immobilized or synthesized. In preferred embodiments, the reaction regions include synthesis frits, pads, resins, or the like.

The solutions delivered to the individual reactant regions of the support matrix flow through the reaction regions to waste disposal regions, recycling tank(s), separators, etc. In some embodiments, the reaction solutions simply pass through the reaction regions under the influence of gravity, while in other embodiments, the solutions are pulled or pushed through the reaction regions by vacuum or pressure.

The individual reaction regions **1004** of the support matrix are separated from one another by walls or gaskets **1006**. These prevent the reactant solution in one reaction region from moving to and contaminating adjacent reaction regions. In one embodiment, the reaction regions are defined by tubes which may be filled with resin or reaction mixture. The gasketing allows close contact between the support matrix **1002** and a "mask" (not shown). The mask serves to control delivery of a first group reactant solutions through predetermined lines (tubes) to a first set of reaction regions. By ensuring close contact between the delivery tubes **1000**, the mask, and the support matrix **1002**, the probability that reaction solutions will be accidently added to the wrong reaction site is reduced.

After each process step, the mask can be changed so that a new group reactants is delivered to a new set of reaction regions. In this manner, a combinatorial strategy can be employed to prepare a large array of polymers or other compounds. In other embodiments, mechanisms other than masks can be employed to block the individual delivery tubes. For example, an array of control valves within the tubes may be suitable for some embodiments.

By adjusting the thickness of the synthesis support matrix, the quantity of immobilized material in the reaction regions can be controlled. For example, relatively thin support synthesis matrices can be used to produce small amounts of surface bound oligomers for analysis, while thicker support matrices can be used to synthesize relatively large quantities

In fact, the overlapping nature of the circles and channels described by Winkler *et al.* are well suited for synthetic methods, where the overlapping monomers provide for combinatorial libraries, but are not suited for the deposition of a single polypeptide. Such intersections of previous or subsequent channels (which are the means by which multiple, distinct, polymers are synthesized) would introduce undesirable contamination for the deposition of long polypeptides.

of oligomers which can be cleaved from the support for further use. In the latter embodiment, a collector having dimensions matching the individual synthesis supports can be employed to collect oligomers that are ultimately freed from the reaction matrix.

To illustrate the ability of this system to synthesize numerous polymers, a square synthesis matrix measuring 10 cm along each side and having 5 mm reaction regions separated by 5 mm wide gaskets provides 100 individual syntheses sites (reaction regions). By reducing the size of the reaction regions to 2.5 mm on each side, 400 reactions regions become available.

While linear grooves are shown herein in the preferred aspects of the invention, other embodiments of the invention will provide for circular rings or other shapes such as circular rings with radial grooves running between selected rings. According to some embodiments, channel blocks with different geometric configurations will be used from one step to the next, such as circular rings in one step and linear stripes in the next. FIG. 13*a* illustrates one of the possible arrangements in which the channels **409** are arranged in a serpentine arrangement in the channel block **407**. Through appropriate translation and/or rotation of the channel block, polymers of desired monomer sequence are formed at the intersection of the channels during successive polymer additions, such as at location **501**, where the intersection of a previous or subsequent set of channels is shown in dashed lines. FIG. 13*b* illustrates another arrangement in which channels (in this case without flow paths **413**) are provided in a linear arrangement, with groups **503** and **505** located in adjacent regions of the substrate and extending only a portion of the substrate length.

In some embodiments of the invention, the various reagents, such as those containing the various monomers, are not pumped through the apertures **413**. Instead, the reagent is placed in one of the grooves, such as the grooves **409** shown in FIG. 13*b*, filling the groove. The substrate is then placed on top of the channel block, and the exposed portions of the substrate are permitted to react with the materials in the grooves. In preferred embodiments, the channels are of the same width as the raised regions between the channels. According to these embodiments, the substrate may then be moved laterally by one channel width or an integer multiple of a channel width, permitting reaction with and placement of monomers on the regions between the channels in a previous coupling step. Thereafter, the substrate or channel block will be rotated for the next series of coupling steps.

In preferred embodiments, the process is repeated to provide more than 10 different polymer sequences on the surface of the substrate. In more preferred embodiments, the process is repeated to provide more than 10^2, 10^3, 10^4, 10^5, 10^6, or more polymer sequences on a single substrate. In some embodiments the process is repeated to provide polymers with as few as two monomers, although the process may be readily adapted to form polymers having 3, 4, 5, 6, 10, 15, 20, 30, 40, 50, 75, 100 or more monomers therein.

It can clearly be seen that the context of col. 17, lines 49-58 refers to the process of synthesizing polymers on a substrate, varying the position and composition of monomers, in order to achieve a desired density of spots. However, such methods are not applicable to polypeptides of greater than at least 50 amino acids in length.

As was previously discussed by Applicants' response of June 11, 2002, polypeptides of at least 50 amino acids in length cannot be synthesized *in situ* to provide for a homogeneous spot of a single peptide. The research article Fodor *et al* (*Science* 251:767-773, 1991), previously provided, describes the method of reacting monomers on a substrate surface to generate polymers. The Fodor paper shows light directed synthesis of two pentapeptides YGGFL and PGGFL on the surface of a substrate, shows that the peptides have been correctly synthesized, and further shows a ten-step binary synthesis of peptides of a range of sizes, up to 10 amino acids in length.

Fodor, on page 771, second paragraph of the first column states: "The net coupling yield *per cycle* in these experiments is typically between 85 and 95 percent." and further recites, in reference 9, the rigorous methods that were used to derived these figures. Therefore, each time a residue is added to a growing polypeptide chain using this method, it is added with an efficiency of 85-95%.

For the purposes of the following discussion, it will be assumed that the coupling efficiency of each cycle is 90%, the average of 85% and 95%. Using the above information, simple algebra teaches that the synthesis of a polypeptide using these methods becomes less and less efficient. For example, assuming the first amino acid is coupled to the substrate is 100% efficient, the synthesis of a two-mer polypeptide will be 90% efficient, the synthesis of a four-mer polypeptide will be 73% (0.9 x 0.9 x 0.9), the synthesis of a 10-mer polypeptide will be 34% (i.e. 0.9^{9}), the synthesis of a 20-mer polypeptide will be 13% (i.e. 0.9^{19}) efficient, the synthesis of a 35-mer polypeptide will be 2.5% (i.e. 0.9^{34}) efficient, and the synthesis of a 50-mer polypeptide will be 0.5% (i.e. 0.9^{49}) efficient. Thus, using an average of 90% coupling efficiency, if a 50-mer is synthesized using the in situ synthesis method, only 0.5% of the polypeptides will have the correct sequence. In other words, synthesis of a 50-mer using this method will result in a heterogeneous mixture of polypeptides, only 5 molecules in a 1000 of which will have the correct sequence.

At this level, the method ceases to be functional, and is no longer useful for synthesizing a selected polypeptide onto a substrate. This effect is demonstrated in the Fodor paper, in which it is noted that no polypeptide of over 7 residues in length was highly bound by a specific

antibody (page 771, second column, second paragraph), despite at least one of the polypeptides having a sequence that should have bound to the antibody.

The methods of Winkler *et al.* are designed for the synthesis of polymers on a substrate, and are not adapted to provide the microarrays taught by Applicants. The Office Action states that Winkler *et al.* teach that the peptides are antibodies or antigens. Applicants respectfully submit that Winkler *et al.* teach that antibodies can be studied by the methods of the invention, not that antibodies are provided in a microarray format. The cited section of the patent is under the heading that reads "Specific examples of receptors which can be investigated by this invention". The further discussion of antibodies in the context of the Winkler invention clearly demonstrates how they are used (col. 17, line 58 to col. 18, line 6):

> According to preferred embodiments, the array of polymer sequences is utilized in one or more of a variety of screening processes, one of which is described in copending application U.S. Ser. No. 796,947, filed on Nov. 22, 1991 and incorporated herein by reference for all purposes. For example, according to one embodiment, the substrate is then exposed to a receptor of interest such as an enzyme or antibody. According to preferred embodiments, the receptor is labelled with fluorescein, or otherwise labelled, so as to provide for easy detection of the location at which the receptor binds. According to some embodiments, the channel block is used to direct solutions containing a receptor over a synthesized array of polymers. For example, according to some embodiments the channel block is used to direct receptor solutions having different receptor concentrations over regions of the substrate.

It is clearly understood by one of the skill in the art that antibodies or other receptors are brought into contact with an array of polymer sequences; the antibodies are not the polymers of the sequence. This is evident by the previous discussion of inefficient synthesis of polypeptides *in situ*. Antibodies are large, complex multimeric proteins, containing multiple disulfide linkages. One of skill in the art cannot synthesis an array of functional antibody molecules on a substrate using the methods taught by Winkler *et al.*

In view of the above remarks, Applicants respectfully submit that the presently claimed invention is not anticipated by the teachings of Winkler *et al.* Withdrawal of the rejection is requested.

Claims 10, 13-16, 18, 31 and 33-37 have been rejected under 35 U.S.C. 102(a) as unpatentable over Gordon *et al.* (GB 2099578) and Chang, U.S. Patent no. 4,829,010.

Applicants respectfully submit that the presently claimed invention is not taught or suggested by the cited combination of references. The present claims have been amended to clarify the size and spacing of the regions of polypeptides that are provided on an array, wherein the array comprises 1000 or more discrete regions of distinct polypeptide per cm^2 of slide wherein discrete regions have a diameter of from 20 to 200 μm.

Gordon *et al.* is stated to teach an array of discrete polypeptides comprising 1000 or more discrete regions of distinct polypeptides/cm^2. The Examiner cites page 11, lines 13-14 as evidence of this teaching.

Applicants respectfully submit that the reference fails to teach an array as set forth in the presently claimed invention, where at least 1000 discrete regions are present on a slide. At page 11, Gordon *et al.* teaches various possible spot diameters, where the smallest, which arrive from a 100 nl volume, are 0.3 mm in diameter. The document then goes on to state that "If Millipore sheets with a grid are used, the ink is sufficiently hydrophobic that the liquid does not spread beyond the printed squares. The intrinsic resolving power of the microdot system is clearly well below the size of the smallest volume that can be applied with pipetting devices, namely ~0.3 mm."

Applicants respectfully note several important facts stated by Gordon *et al.* The first is that the arrays in question are pipetted onto a porous sheet. In fact, the patent application notes at page 2 that "An essential feature of this present invention is the high binding capacity of microporous sheets." One of skill in the art would understand that the particular substrate utilized by Gordon *et al.* is not a slide, which has a non-porous surface, and that the possibility of achieving a high density array using the methods of Gordon *et al.* require the use of the specific high capacity microporous sheets.

Further, the claims as presently amended recite discrete regions of 20 to 200 μm. It is clear from the statements made by Gordon *et al.* that the prior art does not teach one of skill in the art how to create a region with a diameter less than 0.3 mm.

The present invention is based on Applicants invention of a method for using a reagent-dispensing device to precisely deposit very small amounts of a protein solution on a planar support, which has provided the means to achieve high density arrays of polypeptides greater than 50 amino acids in length on slides. Claims 10, 13-16 and 18 specifically recite the use of such a reagent-dispensing device, and specifically recite that the dispensed volume is 0.002 and 2 nl of solution. Clearly, the volume of reagent dispensed by the methods of Applicants is far smaller than that which can be achieved using the methods of Gordon *et al.*

The teachings of Chang do not remedy the deficiencies of the primary reference. Chang fails to teach arrays comprising 1000 or more discrete regions of distinct polypeptide per cm^2 of slide wherein discrete regions have a diameter of from 20 to 200 μM. As set forth in Chang *et al.* (col. 3, lines 40-44), "The volume of the droplet, of course, determines the size of the antibody-coated area. Preferably the volume should range between 0.005-0.5 μl to yield antibody-coated dots with diameters of 0.25 mm - 1.0 mm." Chang therefore fails to teach microarrays of polypeptides having a diameter of 20 to 200 μm, and their arrangement in a high density array.

Chang further fails to teach methods whereby a reagent-dispensing device deposits 0.002 - 2 nl of solution on a planar surface. The lowest volume taught by Chang is 5 nl., and even that volume can only be estimated using the methods of the reference. It is stated (col. 6, lines 34-37) that "Amounts larger than 0.05 μl could be measured delivered. The amount of solution in droplets smaller than 0.05 μl was estimated."

In addition to filing to teach the particular sizes of discrete regions and volumes claimed by Applicants, one of skill in the art is not motivated to increase the density of arrays by combining the teachings of Gordon *et al.* with the teachings of Chang, because neither reference teaches how to achieve controlled deposition of small volumes of polypeptides. As shown in Table 2 of Chang, in a 1 cm^2 matrix, a grid containing 400 dots of 0.25 mm each can be achieved. Combining the technology of Chang (*i.e.* 400 dots of .25 mm) with that of Gordon *et al.*, (which states that the smallest volume that can be applied results in a 0.3 mm diameter) would not result in an array with a higher density.

Indeed, in order to maintain discrete regions, one must have spacing between the regions. Where the regions are 0.3 mm in diameter, there is physically not enough space to provide 1000 discrete regions, as the physical size would require that the regions nearly touch each other. Given the diameters and volumes that are used, the 400 regions/cm^2 of Chang is at the upper limit of what can be realistically achieved, as this geometry provides for 20 spots of 250 μm/linear centimeter, spaced 250 μm apart. It is noted by Applicants (page 7, lines 1-5) that the present specification suggests that the regions be separated from other regions by the diameter.

In view of the above amendments and remarks, Applicants respectfully submit that the presently claimed invention is not made obvious by the cited combination of references. Withdrawal of the rejection is requested.

Claims 10, 13-16 and 18 have been rejected under 35 U.S.C. 103(a) as unpatentable over Gordon *et al.* and Chang as applied above and further in view of Beattie. Applicants respectfully submit that the presently claimed invention is not made obvious by the cited combination of references.

The rejected claims recite that the microarray is created by loading an aqueous solution of a selected polypeptide of at least 50 amino acids in length in a reagent-dispensing device having an elongate capillary channel adapted to hold a quantity of the reagent solution and having a tip region at which the solution in the channel forms a meniscus, and tapping the tip of the dispensing device against a surface of a planar solid support at a defined position, with an impulse effective to break the meniscus in the capillary channel and deposit a selected volume between 0.002 and 2 nl of solution on the surface of the planar solid support. The cited art fails to teach an array created by the methods of the invention, and fail to teach an array having the specific geometry set forth by applicants.

Applicants note that the substrate of Beattie is not a solid planar surface, but a substrate comprising "a multiplicity of discrete channels", and where the binding reagent is not on the flat surface but on the walls of the channels, which are curved surfaces. As stated by Beattie, a "variety of materials can be immobilized or fixed to the glass surfaces within the channels of the NCG array, to yield a high surface area to volume ratio[1]", which is not found in a planar surface. The methods of Beattie *et al.* cannot teach a planar array having a defined diameter, because the arrays of Beattie *et al.* are immobilized or fixed to the channel walls, and thus are not a planar region.

Further, the microfluidic devices utilized in the methods of Beattie *et al.* do not deliver fluids by the tapping and deposition method recited in the present claims, but with a microfluidic jet (col. 14, lines 32-35). Such micro-jet devices operate by a different mechanism, and are not expected to generate the same array on a planar surface as arrays produced by the methods of the present invention. In fact, the methods of Beattie *et al.* utilize a flow-through vacuum system for binding DNA probes or targets (example 6), a modification that is not possible where the substrate is a non-porous slide. Because the microfluidic devices of Beattie *et al.* are utilized with a porous substrate, not a solid slide, one of skill in the art is not motivated to combine the microfluidic device with the teachings of Chang or Gordon *et al.* in order to achieve the presently claimed invention.

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[1] column 9, lines 57-59)

Beattie specifically teaches away from the use of flat, *i.e.* planar, substrates, stating that "Another limitation of these prior art approaches is the fact that a flat surface design introduces a rate-limiting step in the hybridization reaction, i.e., diffusion of target molecules over relatively long distances before encountering the complementary probes on the surface. In contrast, the microfabricated apparatus according to the present invention is designed to overcome the inherent limitations in current solid phase hybridization materials, eliminating the diffusion-limited step in flat surface hybridizations and increasing the cross sectional density of DNA.[2]"

The Office Action states that Beattie *et al.* teaches the use of a slide. Applicants respectfully disagree. Beattie *et al.* is clearly and resolutely directed to the use of a porous material having functional wells. The citation to Beattie in the Office Action reads as follows:

> Initial lamination process development is carried out using unablated polymeric material (or alternatively using glass slides and/or silicon wafers). Cure temperature, pressure and fixturing are optimized during this process development. Thereafter, the optimized processing parameters are employed to laminate both nonporous wafers and polymeric arrays. The final lamination is done such that the alignment of the two layers creates functional wells.

One of skill in the art, upon reading the specification of Beattie et al., can be in no doubt that the reference does not intend arrays to be produced on a flat surface, but rather on a microfabricated apparatus having numerous channels for binding of the DNA.

Applicants respectfully submit the presently claimed invention is not taught or suggested by the cited combination of references. Withdrawal of the rejection is requested.

Claims 10, 13-15, 18, 31 and 33-35 have been rejected under 35 U.S.C. 103(a) as being unpatentable over Beattie *et al.* as defined by Zubay in view of Chang. Applicants respectfully submit that the presently claimed invention is not made obvious by the cited combination of references.

For the reasons described above, Applicants respectfully submit that Beattie *et al.* does not teach microarrays on a slide – only that the arrays of the Beattie invention could utilize a slide in initial fabrication prior to creation of the wells that are central to the Beattie invention. Indeed, one need only read the title of the patent, "Microfabricated, Flowthrough Porous Apparatus for Discrete Detection of Binding Reactions" to understand that Beattie et al. does not teach microarrays on slides, but rather on a flow-through porous apparatus.

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[2] (column 3, lines 18-26)

Beattie *et al.* does not teach the dimensions of discrete regions taught by Applicants, because Beattie et al. does not teach a planar array, but rather an array where the sides of wells are coated with DNA.

Further, with respect to Claims 10, 13-15 and 18, Beattie *et al.* does not teach methods where a dispensing device taps the surface of a planar solid. Indeed, since the substrate of Beattie *et al.* comprises wells, (*i.e.* an open space) it would be physically impossible to utilize the teachings of Beattie and derive a method involving tapping the tip of the dispensing device against a surface of a planar solid support at a defined position.

Applicants respectfully submit that there is no reason to combine the teachings of Chang, which may utilize a slide, with the teachings of Beattie *et al.*, which teach that a flat surface design is undesirable. The combination of the two references is clearly a case of hindsight – picking and choosing from disparate elements in order to spin together Applicants invention, where the references themselves clearly do not suggest being combined.

One of skill in the art would read Beattie *et al.* as teaching a particular flow-through apparatus, in which a solution is sprayed into a well in order to provide a greater surface area for binding. Such teachings are not reasonably combined with the pipetting device of Chang *et al.*

Applicants respectfully submit that the presently claimed invention is not made obvious by the combination of cited references. In view of the above amendments and remarks, withdrawal of the rejection is requested.

Claims 16 and 36 have been rejected under 35 U.S.C. 103(a) as being unpatentable over Beattie as defined by Zubay in view of Chang as applied above, and further in view of Van Ness *et al.* Van Ness et al. specifically teach a cationic film for convenient attachment of polypeptides.

Applicants respectfully submit that the secondary reference does not correct the deficiencies of the primary reference. Van Ness *et al.* fails to teach or suggest a planar microarray on a slide comprising at least 10^3 different polypeptides/cm^2, and wherein discrete regions have a diameter of from 20 to 200 μm. As described above, one of skill in the art would not reasonably combine the teachings of Beattie *et al.*, which require a flow-through apparatus, with the teachings of Chang *et al.*, which provide for a low-density planar array. Van Ness *et al.* fail to remedy the deficiencies of the primary references. Van Ness *et al.* teach particular coatings, but not their use in the preparation of a microarray according to the presently claimed invention.

Applicants respectfully submit the cited combination of references do not make obvious the presently claimed invention. Withdrawal of the rejection is requested.

Applicant respectfully requests that a timely Notice of Allowance be issued in this case.

The Commissioner is hereby authorized to charge any underpayment of fees associated with this communication, including any necessary fees for extensions of time, or credit any overpayment to Deposit Account No. 50-0815, order number STAN-128.

Respectfully submitted,
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